REMARKS

Claims 1-10, 13-22 are pending. Claims 1-9 and 17-22 were previously withdrawn by the Examiner. Claim 10 has been amended to delete the phrase "derivatives of" and to correct a typographical error. Support is found throughout the specification, and no new matter has been added.

Rejections Under 35 U.S.C. § 112

Claims 10 and 13-16 were rejected under 35 U.S.C. 112, first paragraph for alleged failure to comply with the written description requirement due to recitation of "derivatives of" chelating agents or chelates of radionuclides. While Applicants disagree with the Examiner's position, solely to expedite prosecution, Applicants have canceled this language from the claims. Thus Applicants submit that this rejection should be withdrawn.

Rejections Under 35 U.S.C. § 102

Applicants are grateful for the withdrawal of the rejection of claims 10-13 and 15 under 35 U.S.C. 102 for alleged anticipation by Maurer et al WO 02/056907 ("Maurer").

Rejections Under 35 U.S.C. § 103

Applicants are grateful for the withdrawal of the rejection of claims 14 and 16 under 35 U.S.C. 103 for alleged obviousness over Maurer as evidenced by Cruse and Lewis, Illustrated Dictionary of Immunology, Boca Raton, FL 1995 ("Cruse and Lewis").

Claims 10 and 13-16 were rejected for alleged obviousness over Liu et al., Journal of Labelled Compounds and Radiopharmaceuticals 1998; XLI: 37-45 ("Liu") in view of Getz et al., (Analytical Biochemistry 1999;273:73-80) ("Getz") and Maurer as evidenced by Cruse and Lewis. Applicants respectfully traverse.

"The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1396 (2207) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit." MPEP Section 2143.

"The rationale to support a conclusion that the claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art." 83 UDPQ2d at 1395 and MPEP Section 2143. Further, a prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. (MPEP 2144.09).

Applicants respectfully assert that the combination of the cited references does not teach or suggest all of the claim limitations and that the claimed compounds possess unexpectedly superior properties. Therefore, applicants respectfully traverse the § 103 rejection.

As the Examiner admits (OA, p. 5), Liu teaches direct labeling[1] of monoclonal antibodies and thus does not teach a conjugate between a Fab fragment and a recited molecular entity imparting diagnostic utility as required by the claims. Furthermore, Liu fails to disclose use of TCEP as the reducing agent as required by the claims and there is no mention of the need for a selective reduction (intra- versus inter-chain disulfide bonds) as required in the claimed process. Moreover, on page 42, lines 8-11 Liu concedes that the directly labeled Fab fragment is

[1] In Liu an antibody was labeled directly with 99mTc, in the absence of a chelating agent as required by the instant claims. Liu also discloses an attempt to directly label a Fab fragment with 99mTc (again in the absence of the chelator as required by the instant claims), but reports that

not homogeneous and thus is not suitable for biological or clinical applications. Clearly Liu does not disclose or suggest the claimed process which provides for a conjugate with a controlled stoichiometry of conjugation (e.g. the stoichiometric molar ratio of molecular entity to Fab fragment in the conjugates is in the range from 0.95 to 1.05 or in the range from 1.95 to 2.05) due to the selective and quantitative reduction of the inter-chain disulfide bond of the Fab fragment by TCEP in the recited range.

Being able to control the stoichiometric ratio during conjugation is of the utmost importance as it allows for chemically defined conjugated diagnostic compounds, in comparison to the heterogeneous mixture of compounds obtained according to Liu, wherein each of the compounds in the obtained mixture may have its own stoichiometry of substitution and thus, the claimed stoichiometric ratios cannot be. This deficiency is not remedied by the other cited references.

Like Liu, Getz fails to teach or suggest the conjugate of a Fab fragment and a recited molecular entity imparting diagnostic utility required by the claims. Moreover, Getz is directed to reduction of myosin and fails to teach or suggest use of TCEP for reduction of disulfide bonds in antibodies, let alone the reduction of inter-chain disulfide bonds in Fabs as required by the method of the claims.

Maurer fails to remedy these deficiencies. Maurer does not disclose a process for preparing a chemical conjugate between an immunoglobulin Fab fragment and a diagnostic moiety as defined in the claims. Maurer is directed to producing conjugates for vaccines, a therapeutic utility, and neither teaches nor suggests the recited diagnostic conjugates.

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the attempt was unsuccessful as the labeled Fab was "not a singular structure and may not be suitable for further biological or clinical applications." Maurer, p. 42.

Moreover, Maurer fails to teach or suggest the claimed process for the preparation of a diagnostic entity with a controlled stoichiometry of conjugation (e.g. the stoichiometric molar ratio of molecular entity to Fab fragment in the conjugates is in the range from 0.95 to 1.05 or in the range from 1.95 to 2.05) via selective and quantitative reduction of the Fab inter-chain disulfide bonds. Indeed, Example 16 of Maurer establishes that each of the successful couplings between the Fab fragment and the protein (see lanes 5-8 and lanes 10-12 of figure 21) results in a complex mixture in which only a portion includes the desired conjugate (with average MW of 40 kDa, shown by an arrow in figure 21). Indeed, these mixtures include significant amounts of uncoupled Fab fragments (MW 25kDa) and/or other undesired compounds, highlighting the inability of the Maurer method to control stoichiometry, and requiring extensive, expensive and impractical separation methods to isolate the derivative of interest from the complex mixture containing it. Contrary to the Examiner's assertion at page 6, Example 16 of Maurer establishes that far from being 1:1, the stoichiometric ratio of Maurer's method is uncontrolled and thus very variable. Moreover, in Maurer this lack of stoichiometric control occurs regardless of the reducing agent used (TCEP or DTT) and regardless of the concentrations used – in each case Maurer wound up with a complex mixture resulting from an inability to control the stoichiometry. See e.g., Fig. 21. Thus, contrary to the Examiner's assertion (OA, p. 6), based on Maurer, one skilled in the art would have no motivation to vary the conditions for TCEP reduction and certainly no expectation of success in controlling the stoichiometry of a diagnostic conjugate by doing so.

In contrast, in the present invention, the claimed method unexpectedly yields controlled stoichiometry of substitution through the selective and quantitative reduction of the inter-chain disulfide bond of a Fab fragment using TCEP so as to provide for two sulfhydryl

groups to be then reacted with the diagnostic moiety or moieties bearing free sulfhydryl reactive groups. As shown in lanes 2, 4 and 6 of Fig. 3, homogeneous products are formed, from a pre-determined, controlled stoichiometry of conjugation that greatly reduces any impurities and allows the desired product to be obtained from a much simpler mixture. See, e.g. p 16, lines 8-23. Neither the method nor the advantages are taught or suggested by Maurer alone or in combination with Liu and/or Getz.

The secondary reference Cruse and Lewis fails to remedy the deficiencies of Maurer, Liu and Getz. Indeed, it was cited by the Examiner simply for the molecular weight of the Fab of Maurer and fails to teach or suggest the claimed methods or the recited conjugates.

In sum, whether taken alone or together, the cited references fail to teach or suggest the claimed methods which provide diagnostic conjugates of controlled stoichiometry and specified stoichiometric ratio through the selective and quantitative reduction of the inter-chain disulfide bond of a Fab fragment using TCEP at concentrations ranging from 0.1 to 10 mM.

Finally, Applicants note that they are confused by the Examiner's statement that "one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by Lui [et al. sic - Liu] to include TCEP as the reducing agent in view of the teachings of Getz et al. and Maurer et al., one would achieve a method for reduction of a fab fragment for direct labelling with 99mTc." OA, p. 6. As explained supra, the claimed is not directed to direct labelling of an antibody like Liu, but rather to a method of preparation of a conjugate between a Fab and a recited molecular entity such as a chelate of a radionuclide of controlled and recited stoichiometry. Thus, even if the Examiner's statement were true (and Applicants submit it is not), it does not establish the obviousness of Applicants' claimed method.

Moreover, for the reasons set forth above, the combination of the cited references does not teach or suggest all of the claim limitations and the claimed compounds possess unexpectedly superior properties.

In view of the present amendments and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

No fee is believed to be necessary in connection with the filing of this Amendment and Response to Restriction Requirement. However, if any additional fee is necessary, applicant hereby authorizes such fee to be charged to Deposit Account No. 50-2168.

Respectfully submitted,

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